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Treatment of refractory adrenocortical carcinoma with thalidomide: Analysis of 27 patients from the European Network for the Study of Adrenal Tumours Registry

Matthias Kroiss[§] (1), Timo Deutschbein[§] (1), Wiebke Schlötelburg (2), Cristina L. Ronchi (1), Ségolène Hescot (3), Daniela Körbl (1), Felix Megerle (1), Felix Beuschlein (4,5), Bruno Neu (6)*, Marcus Quinkler (7), Eric Baudin (3), Stefanie Hahner (1), Anke Heidemeier (2), Martin Fassnacht (1, 8)

(1) Department of Internal Medicine I, Endocrine and Diabetes Unit, University Hospital Würzburg, University of Würzburg, Germany; (2) Department of Radiology, University Hospital Würzburg, University of Würzburg, Germany; (3) Gustave Roussy, Université Paris Sud, France; (4) Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany; (5) Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitätsspital Zürich, Zürich, Switzerland; (6) Second Department of Medicine, Acedemic Teaching Hospital Landshut Achdorf, Germany (7) Endocrinology in Charlottenburg,, Berlin, Germany; (8) Comprehensive Cancer Center Mainfranken, University of Würzburg, Germany.

[§] M.K. and T.D. contributed equally to this work

Short running title: Thalidomide in advanced adrenocortical carcinoma.

Key words: adrenal, adverse events, cancer, efficacy, follow-up, outcome, progression, side-effects, staging, toxicity, treatment

Corresponding author: Matthias Kroiss, M.D., PhD
Department of Internal Medicine I
Endocrine and Diabetes Unit
University Hospital Würzburg
University of Würzburg
Oberdürrbacher Str. 6
97080 Würzburg
Germany
Phone: +49-(0)931-201-39740
Fax: +49-(0)931-201-639740
Email: Kroiss_m@ukw.de

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Abbreviations:	ACC, adrenocortical carcinoma; CT, computed tomography; CTC, Common Toxicity Criteria; ECOG, Eastern Cooperative Oncology Group; ENSAT, European Network for the Study of Adrenal Tumours; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours
Quick summary:	This retrospective multi-center study of 27 adrenocortical carcinoma (ACC) patients evaluated salvage treatment with thalidomide. Best response was stable disease in two cases. Wide-spread use of thalidomide as a salvage therapy in ACC is not advisable.

Abstract

Objective: Adrenocortical carcinoma (ACC) is a rare malignancy with a dismal prognosis. In advanced stages, tumour control by mitotane and cytotoxic chemotherapy is often temporary and salvage treatments are warranted.

Methods: Retrospective cohort study of participants in the prospective European Networks for the Study of Adrenal Tumours (ENSAT) registry. Main outcome measures were best response during treatment, progression-free survival (PFS), both measured according to RECIST 1.1 by two blinded radiologists, and overall survival (OS).

Results: Twenty-seven patients (13 males; median age 44.1 years) progressing after mitotane and a median of 4 further systemic treatments were included. Thalidomide was administered as tolerated with a starting dose of 50 mg and target dose of 200 mg /d. The median interval between treatment initiation and first imaging was 10.5 (4.4-17.5) weeks. The best response to treatment was stable disease (SD, n=2) and progressive disease (n=25), with a median PFS of 11.2 weeks and a median OS of 36.4 weeks. The first patient with SD discontinued treatment due to mild epistaxis and diarrhea after 22.3 weeks. The second patient had SD at the second treatment evaluation after 25.2 weeks and continued thalidomide but then had clinical progression and deceased after 54.3 weeks. In general, thalidomide induced only mild or moderate adverse effects (mainly fatigue and gastrointestinal complaints).

Conclusion: Thalidomide was overall well tolerated but resulted in disease control in only 2/27 (7.4%) patients. In the absence of predictive response markers, thalidomide should only be considered in exceptional cases as a salvage therapy in ACC.

Introduction

Adrenocortical carcinoma (ACC) is an orphan malignancy with a dismal prognosis [1-4]. Complete tumour removal is still the only potentially curative option and is the initial treatment of choice in localized disease [5-7]. While the role of surgery in advanced disease remains controversial [8-11], the adrenostatic agent mitotane is regarded as the cornerstone of medical therapy in advanced disease and in adjuvant treatment of high-grade ACC [12-18]. The first phase III clinical trial in ACC established mitotane plus combination chemotherapy with etoposide, doxorubicin, and cisplatin as standard of care for the treatment of advanced cases [19]. Other cytotoxic chemotherapy regimens include gemcitabine/capecitabine [20,21] and streptozotocin [22]. In tumours refractory to cytotoxic chemotherapy, however, treatment options are still scarce. Over the last decade, several cytotoxic and molecular targeted therapies have been evaluated as potential alternatives [23-28] but failed to reach significant improvement [29]. In the absence of established treatments, thalidomide has attracted some interest. Historically prescribed as a hypnotic agent, it was soon banned due to its high teratogenic potential. Extensive research led to recognition of the anti-angiogenic and immunomodulatory properties of the drug, resulting in its renaissance as an effective therapy for leprosy and multiple myeloma for which it is approved in combination with melphalan and prednisone [30-33]. An encouraging case report published in 2005 showed an impressive tumour response in a female patient with advanced ACC [34]. Another series described a decrease of tumour burden in four of six ACC patients treated with thalidomide (either alone or in combination with other mitotane or systemic chemotherapy [35]. This resulted in subsequent use of thalidomide as an off-label treatment in selected patients suffering from refractory ACC. Unfortunately, however, the success rate of this salvage therapy has never been investigated. Hence, we hereby aimed at determining the efficacy and tolerability of thalidomide in patients with refractory ACC who were prospectively enrolled in the European Network for the Study of Adrenal Tumours (ENSAT) Registry.

Subjects and Methods

Patients

Patients and clinical parameters (e.g. sex, age at initial diagnosis, evidence of hormone excess, size of the primary tumour, tumour stage according to the ENSAT classification [36], Weiss score [37], Ki67 index [38,39], date of documented irresectability and subsequent therapies, presence and number of distant metastases, concomitant treatment with mitotane, and detailed follow-up information) were retrieved from the German ACC Registry and the ENSAT Registry (www.ensat.org/registry). Both registries had formerly been approved by the ethics committee of the University of Würzburg (approval numbers 86/03, and 88/11, respectively). To be included into the study, patient had to fulfill the following criteria at the time of treatment initiation with thalidomide: age ≥18 years, histologically confirmed ACC, written informed consent, refractory and measurable progressive disease at baseline, no prior therapy with thalidomide, treatment with thalidomide for at least 30 days.

Treatment evaluation

In 24 cases (89%), tumour response was radiologically assessed prior to treatment and from the beginning of treatment until tumour progression, using the Response Evaluation Criteria In Solid Tumours (RECIST) guideline version 1.1 for interpretation of imaging results [40]. For this, all imaging studies were individually reviewed in a blinded fashion by two experienced radiologists (A.H., W.S.). Follow-up imaging after initiation of thalidomide was not performed in three patients with severe tumour progression; these cases were only clinically evaluated. Adverse drug effects considered to be treatment related were retrieved from patient records and graded according to the National Cancer Institute Common Toxicity Criteria (CTC) version 4.0. In uncertain cases, the physician who originally supervised the treatment was contacted to clarify potential adverse events. Adverse drug effects at least considered possibly treatment-related are reported in this study.

Statistical analysis

Progression-free survival was defined as the interval between the beginning of thalidomide treatment and the date at which progressive disease was documented at imaging, clinically (e.g. treatment

discontinuation due to severely impaired general condition or adverse effects), or death of any cause. Overall survival was calculated as the time between start of thalidomide and death of any cause or last follow-up. Survival curves were constructed using the Kaplan-Meier method. Continuous variables are presented as the median and range and Kaplan-Meier curves as the median and 95% confidence interval unless otherwise stated. Statistical significance was taken as $p<0.05$. GraphPad Prism 6.0 software (GraphPad Software Inc., San Diego, USA) was used for statistical calculations.

Results

Patient characteristics

At the time of the final analysis (January 2018), 27 patients fulfilling the inclusion criteria were identified (pertinent data are given in Table 1). Patients were treated with thalidomide between 2005 and 2017 in 4 European centers participating in the ENSAT Registry. At the time of treatment initiation, all except one patient had undergone surgical resection (with 13 subjects having at least one surgical re-intervention). Systemic pretreatment was mitotane in all 27 patients (100%); 21 patients (78%) had at least three prior systemic therapies in addition to mitotane (median of 4 further systemic treatments), while three patients (11%) had declined any cytotoxic chemotherapy and were pretreated only with mitotane. The median intervals between initiation of thalidomide and the initial diagnosis of ACC or the first documentation of metastatic disease were 36.0 months (range 6.0 - 98.9 months) and 25.2 months (range 0.0 to 72.5 months), respectively.

Tumour response and survival analysis

Patients were initially treated with a median thalidomide dosage of 100 mg/d (range 50 to 200 mg/d), usually given once daily. Thalidomide was adjusted according to tolerability and toxicity aiming at a target dosage of 200mg/d. In a single patient, thalidomide was reduced from 200 to 100 mg per day because of CTC grade II fatigue. Conversely, dosages were increased in 11 patients to a maximum of 400 mg/d in a single patient. One patient refused to increase the dosage > 50mg/d due to the perceived risk of adverse effects. The median interval between treatment initiation and subsequent staging was

10.5 weeks (range 4.4 to 17.5 weeks). Best response to treatment was stable disease in two patients, whereas 25 patients experienced progressive disease already at the time of their first imaging. The median progression-free survival was 11.2 weeks (range 4.4 to 22.8 weeks, Figure 1). The first patient with stable disease refused continuation of treatment due to mild epistaxis and diarrhea after 22.3 weeks and progressed finally after 34.8 weeks. The second patient had stable disease according to RECIST criteria at the second staging on treatment after 25.2 weeks. This treatment evaluation was performed by 18-fluorodeoxyglucose positron emission tomography (F-18-FDG-PET-CT) and revealed increased tracer uptake of one bone lesion that was previously barely detectable. The patient continued treatment despite clinical suspicion of tumour progression (bone pain) without interim imaging for 41.6 weeks and died from ACC 54.3 weeks after treatment initiation. Of note, prior thalidomide he had progressed to 4 different cytotoxic regimens after a duration of 17 (EDP), 13 (gemcitabine/capecitabine), 9 (streptozotocin), and 26 (trofosfamide) weeks. This patient received a thalidomide dose of only 50 mg/d since he declined a higher dosage. Mitotane had been discontinued before thalidomide.

At the time of evaluation, all patients have deceased and median OS is 36.4 weeks (range 5.1 to 111.1 weeks, Figure 2).

Treatment related toxicity

Retrospective information about tolerability was available in 25 patients (93%). Relatively mild treatment related symptoms (i.e., CTC grades I and II) were observed in 14 patients, whereas 4 patients experienced more severe adverse events (i.e., CTC grade III). For the remaining 7 patients, no treatment-related side-effects were recorded. Details are given in Table 2.

Description of two remarkable cases

We observed only two cases with disease stabilization. In the first patient, thalidomide was stopped due to adverse effects (i.e. epistaxis and diarrhea). The second patient had disease stabilization at the second treatment evaluation and continued treatment without further tumour evaluation until his death in the 42nd week of treatment at a dose of only 50 mg thalidomide. This patient was diagnosed with an ENSAT stage II ACC 4.3 years before initiation of thalidomide. The primary tumour had a very low Ki67 index

of only 2% and a corresponding Weiss score of 4; biochemically, an androgen excess was observed. Despite these features, advanced disease was diagnosed after one year. Apart from local recurrence, metastases were present in both lungs, the peritoneum, and bones (with the latter presenting as diffuse osteolytic metastasis). Of note, extra-osseous tumour lesions were radiologically stable at the first and second radiologic evaluation of thalidomide. However, there was also increasing FDG-uptake in a bone lesion which was retrospectively present at the initial staging on therapy. Bone metastases during continued thalidomide showed clinical progression, resulting in a pathological fracture which required surgical stabilization. Hence, overall disease course was characterized by uncontrolled bone metastases and it is uncertain whether stable disease of measurable tumour lesions really reflected a treatment related effect.

Discussion

After an initial very promising case report published in 2005 [34], our study is the first evaluating the efficacy of thalidomide in ACC. In this series of 27 mostly heavily pre-treated patients, we did not observe clinically significant single-agent activity of this drug. Whereas 25 of 27 patients (93%) experienced clinically or radiologically unequivocal progressive disease at the time of first staging, two patients had stable disease lasting for 25 weeks in one patient.

Over the last few years, systemic therapy for adrenocortical carcinoma has been intensively investigated. In metastatic disease, mitotane alone or in combination with cytotoxic drugs is considered as a first-line treatment. It has recently been confirmed that objective tumour response can be expected up to 20% of selected cases [18]. Cytotoxic chemotherapy is currently regarded as the mainstay of treatment and combination chemotherapy with etoposide, doxorubicin and cisplatin together with mitotane is currently considered as a standard of care according to the first international randomized phase III trial in ACC [19]. Although objective response was observed in 23.2%, progression-free survival is still only 5 months. Other regimens such as gemcitabine/capecitabine [20] result in much lower rates of objective response. Tumour stabilization is seen in ~25% of patients [21], which is similar to the response obtained with streptozotocin [19]. Hence, most patients treated with current chemotherapeutic regimes suffer from insufficiently controlled disease and seek additional treatment options.

Extensive neo-angiogenesis as a hallmark of tumour growth has attracted attention also in ACC. Due to the high expression of vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) in ACC tumour cell lines [41,42], prospective phase II clinical trials have been conducted using the multi-tyrosine kinase inhibitors sunitinib and sorafenib [25,26]. However, results were disappointing and are partly supposed to be related to accelerated metabolism of tyrosine kinase inhibitors through induction of cytochrome P450 3A4 by mitotane [43,44]. It has been argued that thalidomide may be a promising therapeutic alternative for solid tumours since it has both anti-angiogenic and immunomodulatory properties [30-33]. In 2005, the case of a 40-year-old female ACC patient (who experienced a dramatic tumour response to thalidomide) was reported [34]. Since then, some centers have used thalidomide as a salvage treatment in selected patients, but efficacy and tolerability have not been systematically investigated to date.

The present study assessed the efficacy and tolerability of thalidomide in patients with refractory ACC. We identified 27 patients who received off-label treatment with thalidomide. Before the latter was initiated, most of the patients had already been treated with several consecutive therapeutic modalities (e.g. surgery, mitotane, cytotoxic chemotherapy, and radiation therapy).

All remaining patients exhibited progressive disease already at the first staging. A possible explanation for this disappointing results in these patients may be secondary drug resistance acquired during previous therapies. However, administering another salvage therapy after various pretreatments is a common circumstance in patients with refractory ACC. In contrast to many targeted therapies [44], thalidomide is not metabolized and hence reduced drug exposure through mitotane-induced cytochrome P450 is unlikely [45], although drug interaction cannot be finally excluded. Overall, thalidomide treatment was well tolerated but one patient with stable disease declined further treatment after 22.3 weeks due to relatively mild epistaxis and diarrhea (both CTC grade I).

An obvious limitation of our current evaluation is its retrospective design. This brings along variable clinical management including restaging at variable time intervals which hampers comparison of treatment effects. Furthermore, the number of cases in our series is still rather small. However, with 27 patients we would expect an initial signal indicating efficacy if present in a clinically relevant proportion

of patients and this number is similar to those in phase II clinical trials of ACC (e.g. [26,46]). Moreover, it has to be kept in mind that larger series are difficult to collect due to the rarity of ACC. Another relevant bias of the study is selection bias. As thalidomide was usually offered only as salvage therapy after failing several other treatment option, this patient cohort is not representative for all patients with ACC. On one hand, the pre-treatment might have induced - as discussed above - drug resistance, on the other hand, patients, who are still alive after failing these many treatment regimens, have obviously not the most aggressive type of ACC. Stable disease as best response in 2 out of 27 patients (7%) may reflect the natural course of disease.

Absence of response to tyrosine kinase inhibitors in ACC has been previously associated with reduced drug exposure due to strong induction of drug metabolizing cytochrome P450 enzymes by mitotane [43,44]. Although we did not measure thalidomide plasma concentrations, only minimal hepatic metabolism of this drug has been described which renders this possibility rather unlikely. A single published phase I clinical trials combining lenalidomide - a related immune modulatory drug (IMiD) - with the mTOR (mammalian target of rapamycin) inhibitor temsirolimus [47] also included three ACC patients of whom one experienced prolonged disease stabilization. It is unclear whether this effect was due to lenalidomide or temsirolimus since a phase II trial of temsirolimus with the IGF1-receptor antibody cixutumuab demonstrated stable disease >6months in 11/26 patients. In general, results of "IMiDs" in solid tumours were largely disappointing. Since thalidomide was overall well tolerated, one might reason that higher doses of thalidomide may be used in the future. Combination of thalidomide with metronomic chemotherapy such as temozolomide [48] or 5-fluorouracil prodrugs [49]might be another option to achieve better tumour response.

In conclusion, our series provide some evidence that thalidomide has only very modest single-agent activity in patients with refractory advanced ACC. The majority of patients does not benefit from the drug. Thus, there is little reason to recommend use of thalidomide as a monotherapy in ACC as long as molecular or clinical response markers are yet to be discovered.

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Table 1. Clinical characteristics. Abbreviations are: ENSAT, European Network for the Study of Adrenal Tumours.

Characteristic	Number (%) of patients or median (range)
Number of patients	27
Female Sex	14 (52%)
Age at initial diagnosis (years)	44.1 (22.7-64.4)
ENSAT tumour stage at initial diagnosis	
II	13 (48)
III	6 (22)
IV	8 (30)
Main endocrine activity at initial diagnosis	
Glucocorticoid excess	12 (44)
Androgen excess	5 (19)
Mineralocorticoid excess	1 (4)
None or not documented	9 (33)
Surgical interventions (number)	
Median (range)	1 (0-6)
Histopathology	
highest Ki67 (n=24)	
<10%	8 (33)
10-19%	6 (25)
≥20%	10 (42)
Weiss score (n=17)	6 (4-9)
Therapy prior to treatment with thalidomide	
Mitotane	27 (100)
- continued at the time of thalidomide initiation	13 (48%)
- Median plasma level at the time of thalidomide initiation (mg/l, n=13)	14.5 (3.5 – 17.6)
Cytotoxic chemotherapy	24 (89)
- Etoposide, Doxorubicin, Cisplatin	22 (81)
- Streptozotocin	22 (81)
- Gemcitabine, Capecitabine	20 (74)
- Trofosfamide	13 (48)
- Etoposide, Cisplatin	2 (7)
- Etoposide, Carboplatin	1 (4)
- Gemcitabine, Carboplatin	1 (4)
- Doxorubicin, Paclitaxel	1 (4)
Targeted therapy	5 (19)
- Linsitinib	3 (11)
- Sunitinib	2 (7)
Combined cytotoxic and targeted therapy	1 (4)
- Capecitabine, vevacizumab	1 (4)
Radiotherapy	9 (33)
Chemoembolization	4 (15)
Radio frequency ablation	3 (11)
^{131}I-Iodometomidate	1 (4)
None	0 (0)
Interval between the initial diagnosis and thalidomide initiation (months)	
Median (range)	36.0 (6.0-98.9)
Interval between the diagnosis of metastasized ACC and thalidomide initiation (months)	
Median (range)	25.2 (0.0-72.4)
Age at thalidomide initiation (years)	
Median (range)	46.9 (24.2-69.0)

Tumor burden at thalidomide initiation	
Distant metastasis (multiple lesions)	12
Combination of local recurrence and multiple metastases	9
Unknown	6

Table 2. Treatment emergent adverse events. Abbreviations are: CTC, Common Toxicity Criteria.

CTC category	Side-effects (in alphabetical order)	CTC Grade 1 – 2 (n)	CTC Grade 3 - 4 (n)
Blood and lymphatic system	Anemia	1	
Gastrointestinal	Constipation	1	
	Decreased appetite	1	
	Diarrhea	3	
	Ileal obstruction		1
	Nausea	1	
General disorders	Asthenia	5	
	Changes of body weight (loss or gain)	2	
	Edema (limb or trunk)	2	
	Fatigue	11	1
	Pain (any)	4	
Laboratory investigations	Increased creatinine		
Nervous system disorders	Dizziness	1	
	Paresthesia	2	
Respiratory, thoracic and mediastinal	Dyspnea	1	
	Epistaxis	1	
Skin and subcutaneous tissue	Dry skin	1	
	Others (worsening of preexisting psoriasis)		1
Endocrine disorders	Cushing's syndrome	1	
Total		38	3

Figure 1. Kaplan-Meier curve of progression-free survival (PFS) after treatment initiation with thalidomide.

The patient with PID17 discontinued thalidomide after 32 days of treatment because of fatigue. Patient with PID 3 continued thalidomide without follow up imaging beyond the last imaging 22.8 weeks after treatment initiation and was therefore censored for PFS at this time point. He died from ACC after 54.3 weeks.

Figure 2. Kaplan-Meier curve of the overall survival after treatment initiation with thalidomide.